REMARKS

I. Status of the Claims

Claims 19, 20, 23, 25, 28-31, 34-36, 38-40, 42, 43, 46-49, 55, 57-60, 62, 64, 66, and 68-70 are pending and under examination in this application.

Claims 19, 66, and 69 have been amended herewith. Support for the claim amendments can be found throughout the application as filed. No new matter has been added by way of this amendment.

II. Rejections Under 35 U.S.C. §112, First Paragraph, Enablement

Claims 19, 20, 23, 25, 28-31, 34-36, 38-40, 42, 43, 46-49, 55, 57-60, 62, 64, 66, and 68-70 stand rejected for allegedly failing to meet the enablement requirement of 35 U.S.C. § 112, first paragraph (*see,* Office Action, pages 2-5). Applicant respectfully traverses this rejection for the reasons described below.

The test of enablement is whether one reasonably skilled in the art could make or use the invention using the disclosure of the patent application together with information known in the art, without undue experimentation. *United States v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988). The test for enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504 (CCPA 1976). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm"n 1983). An applicant need not have actually reduced the invention to practice prior to filing. *Gould v. Quigg*, 822 F.2d 1074, 1078 (Fed. Cir. 1987). The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it. *Id.* Accordingly, it is not necessary that an application contain an actual experimental demonstration of the claimed methods in order to enable the claims.

As stated in response to the previous Office Action, the application as filed provides sufficient guidance to enable one of ordinary skill in the art to make and use the invention as

claimed, without undue experimentation. For example, the disclosure at page 51, line 16 to page 53, line 6; page 61, line 3 to page 62, line 28; page 75, line 19 to page 81, line 13; Figs. 20 and 21; page 84, lines 2-28; page 88, line 24 to page 89, line 14 of the application as filed provides a sufficient disclosure to enable one of ordinary skill in the art to perform the claimed methods for increasing tolerance in a patient to a graft from an MHC-mismatched donor.

In support of enablement, Applicant previously submitted a post-filing article by Goldberg *et al.* entitled "Enhanced Immune Reconstitution by Sex Steroid Ablation following Allogeneic Hematopoietic Stem Cell Transplantation." As described previously, the data presented in this article demonstrates increased tolerance to transplanted donor cells in castrated mice as compared to non-castrated mice.

The present Office Action, at pages 3-4, asserts that the Goldberg *et al.* article fails to support enablement of the present claims because the publication fails to show tolerance to "another" allogenic graft, stating "the publication shows that there is no change of host response to another graft (tumor) following the allogenic HSC." However, Applicant submits that this result in Goldberg *et al.* is irrelevant to the question of whether the claimed methods are enabled. The pending claims relate to administering cells from a MHC-mismatched donor to increase tolerance to a subsequently administered graft from the same MHC-mismatched donor (*e.g.*, claim 19), or to administering cells that have the same histocompatibility as those of a MHC-mismatched donor to increase tolerance to a subsequently administered graft from the MHC-mismatched donor (*e.g.*, claim 66). In contrast, the engrafted tumor cells (mastocytoma cell line P815 (H-2D) used in Goldberg *et al.* do not constitute a graft from a donor with the same histocompatibility. Tolerance to the graft (tumor) in Goldberg *et al.* would not be expected because the cells administered to induce tolerance are not from the same MHC mismatched donor as the graft (tumor).

In view of the foregoing remarks, Applicant submits that the pending claims are fully enabled. Accordingly, Applicant respectfully requests that this rejection under 35 U.S.C. § 112, first paragraph, enablement, be reconsidered and withdrawn.

III. Rejection Under 35 U.S.C. §102(b)

Claims 19, 20, 23, 25, 28-31, 34-36, 42, 43, 46, 55, 57-59, 62, 64, 66, and 68-70 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Ghalie *et al.* (*Am. J. Hematol.* 42:350-3, 1993) (*see,* Office Action, page 5).

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Ghalie *et al.* fails to teach each every element of amended claims 19, 66, and 69, and thus cannot anticipate claims 19, 66, and 69, or the claims dependent therefrom.

The Office Action asserts that the allogenic bone marrow transplantation disclosed by Ghalie *et al.* meets both the limitation of administering cells from the MHC-mismatched donor and the limitation of providing a graft from the MHC-mismatched donor (*see,* Office Action, page 6).

By this paper, the present claims are amended to more clearly point out that the claimed methods require the sequential administration of "cells" and a "graft." For example, amended claim 19, as presented herein requires administering cells from a MHC-mismatched donor to the patient and subsequently providing a graft from the MHC-mismatched donor to the patient. Ghalie *et al.* teaches only administering cells once, whereas the claimed invention requires on the sequential administration of "cells" followed by the "graft."

Because Ghalie *et al.* does not teach each and every element of the amended claims, it cannot anticipate the instant claims. Accordingly, Applicant respectfully requests that the rejection of the claims under 35 U.S.C. § 102(b) be reconsidered and withdrawn.

IV. Rejection Under 35 U.S.C. §103(a)

Claims 19, 20, 23, 25, 28-31, 34-36, 38-40, 42, 43, 46-49, 55, 57-60, 62, 64, 66, and 68-70 stand rejected under 35 U.S.C. § 103(a) as purportedly being obvious over Mardiney *et al.* (U.S. Patent No. 6,863,885), in view of BBC News (December 1998), and Windmill *et al.* (*Tissue Cell*, 30:104-11, 1998) (*see,* Office Action, page 7).

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

In this case, the combined references do not teach or suggest all claim limitations. The amended claims, as presented herein, require administering cells from a MHC-mismatched donor to the patient and subsequently providing a graft from the MHC-mismatched donor to the patient.

Mardiney *et al.* teaches only administering cells once. This deficiency of Mardiney *et al.* is not remedied by the other references cited in the Office Action, as neither the BBC News article nor Windmill *et al.* teach or suggest the sequential administration of "cells" followed by a "graft."

Furthermore, the art teaches away from the present invention. On page 4, the Office Action cites several references in which surgical or chemical castration allegedly had no influence on graft survival time or graft rejection. The Office Action comments on this "lack of predictability of the art" in rejecting the claims under 36 U.S.C. 112. Thus, the Office Action itself admits that the prior art teaches away from the presently claimed invention. Accordingly, one of skill in the art would not be motivated to combine the Mardiney *et al.* with the BBC News article or Windmill *et al.*, and one of skill in the art would have no reasonable expectation of success in combining the cited references.

Finally, Applicant wishes to note that the Office Action mischaracterizes the BBC News article. The Office Action asserts that the BBC News article "establishes it was known in the art that chemical castration via sex hormones can restore/regenerate thymus function and [may be] useful for patients to accept transplanted organs." This is an unreasonable interpretation of the BBC News article. The BBC News article makes no suggestion that disrupting sex steroid

signaling can be useful for inducing tolerance to a graft. The BBC News article indicates only that patients with AIDS, or patients who are undergoing transplantation of an organ, are immunosuppressed and hence "vulnerable to infection." The BBC News article does not in any way imply that disrupting sex steroid signally would be useful "to accept transplanted organs."

In view of the amendments to the claims presented herein, and the above remarks, Applicant respectfully requests that the rejection of the claims under 35 U.S.C. § 103 be reconsidered and withdrawn.

CONCLUSION

Applicant respectfully requests entry and consideration of this amendment, which places the application in condition for allowance, or in better condition for Appeal.

Applicant hereby petitions for a three-month extension of time to respond to the outstanding Office Action. Please charge the requisite fees to our Deposit Account No. 08-0219. No additional fees are believed to be due in connection with this correspondence. However, if any additional fees are due, please charge the fees due to our Deposit Account No. 08-0219.

This paper is being filed concurrently with a Notice of Appeal and a Supplemental Information Disclosure Statement. In addition, Applicant respectfully requests that the Examiner review and initial previously-filed Supplemental Information Disclosure Statements dated November 2, 2004, January 20, 2005, and April 15, 2008.

If a telephone interview would advance prosecution of the application, the Examiner is invited to telephone the undersigned at the telephone number given below.

Respectfully submitted,

Dated: January 12, 2009

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